

ADUHELM- aducanumab injection, solution

Biogen Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADUHELM™ safely and effectively. See full prescribing information for ADUHELM.

ADUHELM™ (aducanumab-avwa) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (1)

DOSAGE AND ADMINISTRATION

- Titration is required for treatment initiation. (2.1)
- The recommended maintenance dosage is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks. (2.1)
- Obtain a recent (within one year) brain MRI prior to initiating treatment. (2.2, 5.1)
- Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). (2.2, 5.1)
- Dilution in 100 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a 0.2 or 0.22 micron in-line filter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:

- 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial (3)
- 300 mg/3 mL (100 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. (2.2, 5.1)
- Hypersensitivity Reactions: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion of ADUHELM and initiate appropriate therapy. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at least 10% and higher incidence compared to placebo): ARIA-Edema, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and fall. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-833-425-9360 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ADUHELM is indicated for the treatment of Alzheimer's disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

After an initial titration, the recommended dosage of ADUHELM is 10 mg/kg (see Table 1). ADUHELM is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.

Table 1: Dosing Schedule

IV Infusion (every 4 weeks)	ADUHELM Dosage (administered over approximately one hour)
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

2.2 Monitoring for Amyloid Related Imaging Abnormalities

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment. Obtain MRIs prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg). If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H) [see *Warnings and Precautions (5.1)*].

2.3 Resuming ADUHELM After Missed Dose

If an infusion is missed, resume administration at the same dose as soon as possible [see *Dosage and Administration (2.1)*]. Infusions are to be administered every 4 weeks and at least 21 days apart.

2.4 Dilution Instructions

- Use aseptic technique when preparing the ADUHELM diluted solution for intravenous infusion. Each vial is for single-dose only. Discard any unused portion.
- Calculate the dose, total volume of ADUHELM solution required, and the number of vials needed based on the patient's actual body weight. Each vial contains an ADUHELM concentration of 100 mg per mL. More than one vial may be needed for a full dose.
- Select the correct vial(s) for the required volume [see *Dosage Forms and Strengths (3)*].
- Check that the ADUHELM solution is clear to opalescent and colorless to yellow solution. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of ADUHELM from the vial(s) and add to an infusion bag of 100 mL of 0.9% Sodium Chloride Injection, USP. Do not use other intravenous diluents to prepare the ADUHELM diluted solution.
- Gently invert the infusion bag containing the ADUHELM diluted solution to mix completely. Do not shake.

- After dilution, immediate use is recommended. If not administered immediately, store the diluted solution of ADUHELM in 0.9% Sodium Chloride Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 3 days, or at room temperature up to 30°C (86°F) for up to 12 hours.
- Prior to infusion, allow the ADUHELM diluted solution to warm to room temperature.

2.5 Administration Instructions

- Visually inspect the ADUHELM diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Infuse ADUHELM diluted solution intravenously over approximately one hour through an intravenous line containing a sterile, low-protein binding, 0.2 or 0.22 micron in-line filter.
- Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

ADUHELM is a clear to opalescent and colorless to yellow solution, available as:

- Injection: 170 mg/1.7 mL (100 mg/mL) in a single-dose vial
- Injection: 300 mg/3 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

ADUHELM can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment [see *Dosage and Administration (2.2)*]. The safety of ADUHELM in patients with any pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established.

In clinical studies of ADUHELM, the severity of ARIA was classified by radiographic criteria, as shown in Table 2.

Table 2: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity	FLAIR hyperintensity	FLAIR hyperintensity

	confined to sulcus and/or cortex/subcortical white matter in one location < 5 cm	5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

In Studies 1 and 2, ARIA (-E and/or -H) was observed in 41% of patients treated with ADUHELM with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo (111 out of 1087).

ARIA-E was observed in 35% of patients treated with ADUHELM 10 mg/kg, compared to 3% of patients on placebo. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers (42% and 20%, respectively). The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of ADUHELM 10 mg/kg who had ARIA-E, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients. Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. 10% of all patients who received ADUHELM 10 mg/kg had more than one episode of ARIA-E.

ARIA-H in the setting of ARIA-E associated with the use of ADUHELM 10 mg/kg was observed in 21% of patients treated with ADUHELM 10 mg/kg, compared to 1% of patients on placebo. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between ADUHELM and placebo. There was no imbalance in hemorrhage greater than 1 cm between ADUHELM and placebo.

Clinical symptoms were present in 24% of patients treated with ADUHELM 10 mg/kg who had an observation of ARIA (-E and/or -H), compared to 5% of patients on placebo. The most common symptom in patients treated with ADUHELM 10 mg/kg with ARIA was headache (13%). Other frequent symptoms were confusion/delirium/altered mental status/disorientation (5%), dizziness/vertigo (4%), visual disturbance (2%), and nausea (2%). Serious symptoms associated with ARIA were reported in 0.3% of patients treated with ADUHELM 10 mg/kg. Clinical symptoms resolved in the majority of patients (88%) during the period of observation.

Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration, as this is the time the majority of ARIA was observed in Studies 1 and 2. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. If ARIA is observed on MRI in the presence of clinical symptoms, careful clinical evaluation should be performed prior to continuing treatment.

Obtain brain MRIs prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion

(sixth dose of 10 mg/kg) of ADUHELM to evaluate for the presence of asymptomatic ARIA. For patients with radiographic findings of ARIA, enhanced clinical vigilance is recommended. Additional MRIs may be considered if clinically indicated. If radiographically severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule. There are no systematic data on continued dosing with ADUHELM following detection of radiographically moderate or severe ARIA. In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H. In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H. The benefits of reaching and maintaining the 10 mg/kg dose should be considered when evaluating a potential dose suspension.

5.2 Hypersensitivity Reactions

Angioedema and urticaria were reported in one patient in the placebo-controlled period of Studies 1 and 2, and occurred during the ADUHELM infusion. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities [see *Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates

observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of

another drug and may not reflect the rates observed in clinical practice.

The safety of ADUHELM has been evaluated in 3,078 patients who received at least one dose of ADUHELM. In two placebo-controlled studies (Studies 1 and 2) in patients with Alzheimer's disease, a total of 1105 patients received ADUHELM 10 mg/kg [see *Clinical Studies (14)*]. Of these 1105 patients, approximately 52% were female, 76% were White, 10% were Asian, and 3% were of Hispanic or Latino ethnicity. The mean age at study entry was 70 years (range from 50 to 85).

In the combined placebo-controlled and long-term extension periods of Studies 1 and 2, 834 patients received at least one dose of ADUHELM 10 mg/kg once monthly for at least 6 months, 551 patients for at least 12 months, and 309 patients for at least 18 months. In the combined placebo-controlled and long-term extension periods, 5% (66 out of 1386) of patients in the 10 mg/kg dose group withdrew from the study because of an adverse reaction. The most common adverse reaction resulting in study withdrawal in the combined placebo-controlled and long-term extension periods was ARIA-H

superficial siderosis. Table 3 shows adverse reactions that were reported in at least 2% of patients treated with ADUHELM and at least 2% more frequently than in patients on placebo.

Table 3: Adverse Reactions Reported in at Least 2% of Patients Treated with ADUHELM 10 mg/kg and at Least 2% Higher Than Placebo in Studies 1 and 2

Adverse Reaction	ADUHELM 10 mg/kg N=1105 %	Placebo N=1087 %
ARIA-E	35	3
Headache ^a	21	16
ARIA-H microhemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea ^b	9	7
Confusion/Delirium/Altered Mental Status/Disorientation ^c	8	4

^aHeadache includes the adverse reaction related terms headache, head discomfort, migraine, migraine with aura, and occipital neuralgia.

^bDiarrhea includes the adverse reaction related terms diarrhea and infectious diarrhea.

^cConfusion/Delirium/Altered Mental Status/Disorientation includes the adverse reaction related terms confusional state, delirium, altered state of consciousness, disorientation, depressed level of consciousness, disturbance in attention, mental impairment, mental status changes, postoperative confusion, and somnolence.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other aducanumab products may be misleading.

The immunogenicity of ADUHELM has been evaluated using an in vitro assay for the detection of binding anti-aducanumab-avwa antibodies.

In up to 41 months of treatment in the combined placebo-controlled and long-term extension periods of Studies 1 and 2, up to 0.6% (15/2689) of patients receiving ADUHELM once monthly developed anti-aducanumab-avwa antibodies.

Based on the limited number of patients who tested positive for anti-aducanumab-avwa antibodies, no observations were made concerning a potential effect of neutralizing activity of anti-aducanumab-avwa antibodies on exposure or efficacy; however, the available data are too limited to make definitive conclusions regarding an effect on pharmacokinetics, safety, or efficacy of ADUHELM. Quantification of neutralizing anti-aducanumab-avwa antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on ADUHELM use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to female rats through organogenesis had no adverse effect on embryofetal development.

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to female rats throughout pregnancy and lactation had no adverse effects on pre- or postnatal development.

The relevance of these data to humans is limited because aggregated amyloid beta, the pharmacological target of aducanumab-avwa, is not present in rat.

8.2 Lactation

Risk Summary

There are no data on the presence of aducanumab-avwa in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADUHELM and any potential adverse effects on the breastfed infant from ADUHELM or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In Studies 1 and 2, the age of patients ranged from 50 to 85 years, with a mean age of 70 years; 79% were 65 and older, and 32% were 75 and older. There were no notable differences in the incidence of adverse reactions between these age groups, and no additional safety concerns in patients 65 years of age and older compared to younger patients.

11 DESCRIPTION

Aducanumab-avwa is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, and is expressed in a Chinese hamster ovary cell line. Aducanumab-avwa has an

approximate molecular weight of 146 kDa.

ADUHELM (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution for intravenous infusion after dilution supplied in single-dose vials available in concentrations of 170 mg/1.7 mL (100 mg/mL) or 300 mg/3 mL (100 mg/mL) of ADUHELM.

Each mL of solution contains 100 mg of aducanumab-avwa and L-arginine hydrochloride (31.60 mg), L-histidine (0.60 mg), L-histidine hydrochloride monohydrate (3.39 mg), L-methionine (1.49 mg), polysorbate 80 (0.50 mg), and Water for Injection at an approximate pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aducanumab-avwa is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. ADUHELM reduces amyloid beta plaques, as evaluated in Studies 1, 2, and 3 [see *Clinical Studies (14)*].

12.2 Pharmacodynamics

Effect of ADUHELM on Amyloid Beta Pathology

ADUHELM reduced amyloid beta plaque in a dose- and time-dependent manner in Study 1, Study 2, and Study 3, compared with placebo [see *Dosage and Administration (2.1)* and *Clinical Studies (14)*].

The effect of ADUHELM on amyloid beta plaque levels in the brain was evaluated using PET imaging (^{18}F -florbetapir tracer). The PET signal was quantified using the Standard Uptake Value Ratio (SUVR) method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate cortices), compared to a brain region expected to be spared of such pathology (cerebellum). The SUVR was also expressed on the Centiloid scale.

In substudies of Study 1 and Study 2, ADUHELM reduced amyloid beta plaque levels in the brain, producing reductions at both ADUHELM low dose and high dose levels and at both Weeks 26 and 78 ($p < 0.0001$), compared to placebo. The magnitude of reduction was time- and dose-dependent. In the long-term extension of Study 1 and Study 2, a continued decrease in brain amyloid beta plaque levels was observed at Week 132 in patients initially randomized to ADUHELM.

In Study 3, ADUHELM reduced amyloid beta plaque levels in the brain, producing statistically significant dose- and time-dependent reductions compared to placebo in the 3 mg/kg, 6 mg/kg, and 10 mg/kg ADUHELM treatment groups at Week 26, and in all ADUHELM treatment groups at Week 54. Among those dosed with ADUHELM during the placebo-controlled period in Study 3, amyloid beta plaque levels in the brain continued to decline in a time- and dose-dependent manner in the long-term extension period through Week 222.

Effect of ADUHELM on Tau Pathophysiology

ADUHELM reduced markers of tau pathophysiology (CSF p-Tau and Tau PET) and neurodegeneration (CSF t-Tau) in Study 1 and Study 2 [see *Clinical Studies (14)*].

ADUHELM reduced CSF levels of p-Tau in substudies conducted in Study 1 and Study 2. The adjusted mean change from baseline in CSF p-Tau levels relative to placebo was in favor of the ADUHELM low ($p < 0.01$) and high ($p < 0.001$) dose groups at Week 78 in Study 1. Results in Study 2 numerically favored ADUHELM but were not statistically significant.

ADUHELM reduced CSF levels of t-Tau in substudies conducted in Study 1 and Study 2. The adjusted mean change from baseline in CSF t-Tau levels relative to placebo was in favor of the ADUHELM low ($p < 0.05$) and high ($p < 0.01$) dose groups at Week 78 in Study 1. Results in Study 2 numerically favored ADUHELM but were not statistically significant.

Substudies were conducted in both Study 1 and Study 2 to evaluate the effect of ADUHELM on neurofibrillary tangles composed of tau protein using PET imaging (^{18}F -MK6240 tracer). The PET signal was quantified using the SUVR method to estimate brain levels of tau in brain regions expected to be affected by Alzheimer's disease pathology (medial temporal, temporal, frontal, cingulate, parietal, and occipital cortices) in the study population compared to a brain region expected to be spared of such pathology (cerebellum). Data from the substudies were pooled, comprising 37 patients with longitudinal follow-up. The adjusted mean change from baseline in tau PET SUVR relative to placebo at follow-up was in favor of ADUHELM high dose in the medial temporal ($p < 0.001$), temporal ($p < 0.05$), and frontal ($p < 0.05$) brain regions. No statistically significant differences were observed for the cingulate, parietal, or occipital cortices.

Exposure-Response Relationships

Model based exposure-response analyses for Studies 1 and 2 demonstrated that higher exposures to ADUHELM were associated with greater reduction in clinical decline on CDR-SB, ADAS-Cog13, and ADCS-ADL-MCI. In addition, higher exposures to ADUHELM were associated with greater reduction in amyloid beta plaque in Studies 1 and 2. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB was also observed.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ADUHELM were characterized using a population PK analysis with concentration data collected from 2961 subjects with Alzheimer's disease who received ADUHELM in single or multiple doses.

Steady-state concentrations of ADUHELM were reached by 16 weeks of repeated dosing with an every 4-week regimen, and the systemic accumulation was 1.7-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{SS}) of ADUHELM increased dose proportionally in the dose range of 1 to 10 mg/kg every 4 weeks.

Distribution

The mean value (95% CI) for volume of distribution at steady state is 9.63 L (9.48, 9.79).

Elimination

ADUHELM is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. ADUHELM clearance (95% CI) is 0.0159 (0.0156, 0.0161) L/hr. The terminal half-life is 24.8 (14.8, 37.9) days.

Specific Populations

Body weight, age, sex, and race were found to impact exposure to ADUHELM. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment

No studies were conducted to evaluate the pharmacokinetics of ADUHELM in patients with renal or hepatic impairment. ADUHELM is not expected to undergo renal elimination or metabolism by hepatic enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

Intravenous administration of aducanumab-avwa (0, 100, 300, or 1000 mg/kg/week) to male and female rats prior to and during mating and continuing in females to gestation day 7 resulted in no adverse effects on fertility or reproductive performance.

The relevance of these data to humans is limited because aggregated amyloid beta, the pharmacological target of aducanumab-avwa, is not present in rat.

14 CLINICAL STUDIES

The efficacy of ADUHELM was evaluated in two double-blind, randomized, placebo-controlled, parallel group studies (Study 1, NCT 02484547 and Study 2, NCT 02477800) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease, stratified to include 80% Stage 3 patients and 20% Stage 4 patients). The effects of ADUHELM were also supported by a double-blind, randomized, placebo-controlled, dose-ranging study (Study 3, NCT 01677572) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and prodromal or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease, with an enrolled distribution of 43% Stage 3 patients and 57% Stage 4 patients), followed by an optional, dose-blind, long-term extension period.

In Studies 1 and 2, patients were randomized to receive ADUHELM low dose (3 or 6 mg/kg for ApoE ϵ 4 carriers and noncarriers, respectively), ADUHELM high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Both studies included an initial titration period of up to 6

months to the maximum target dose. At the beginning of the study, ApoE ε4 carriers were initially titrated up to a maximum of 6 mg/kg in the high dose group, which was later adjusted to 10 mg/kg.

In Studies 1 and 2, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤ 85 , and a Mini-Mental State Examination (MMSE) score of 24-30. In Study 3, patients were enrolled with a global CDR score of 0.5 or 1.0 and an MMSE score of 20-30. Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

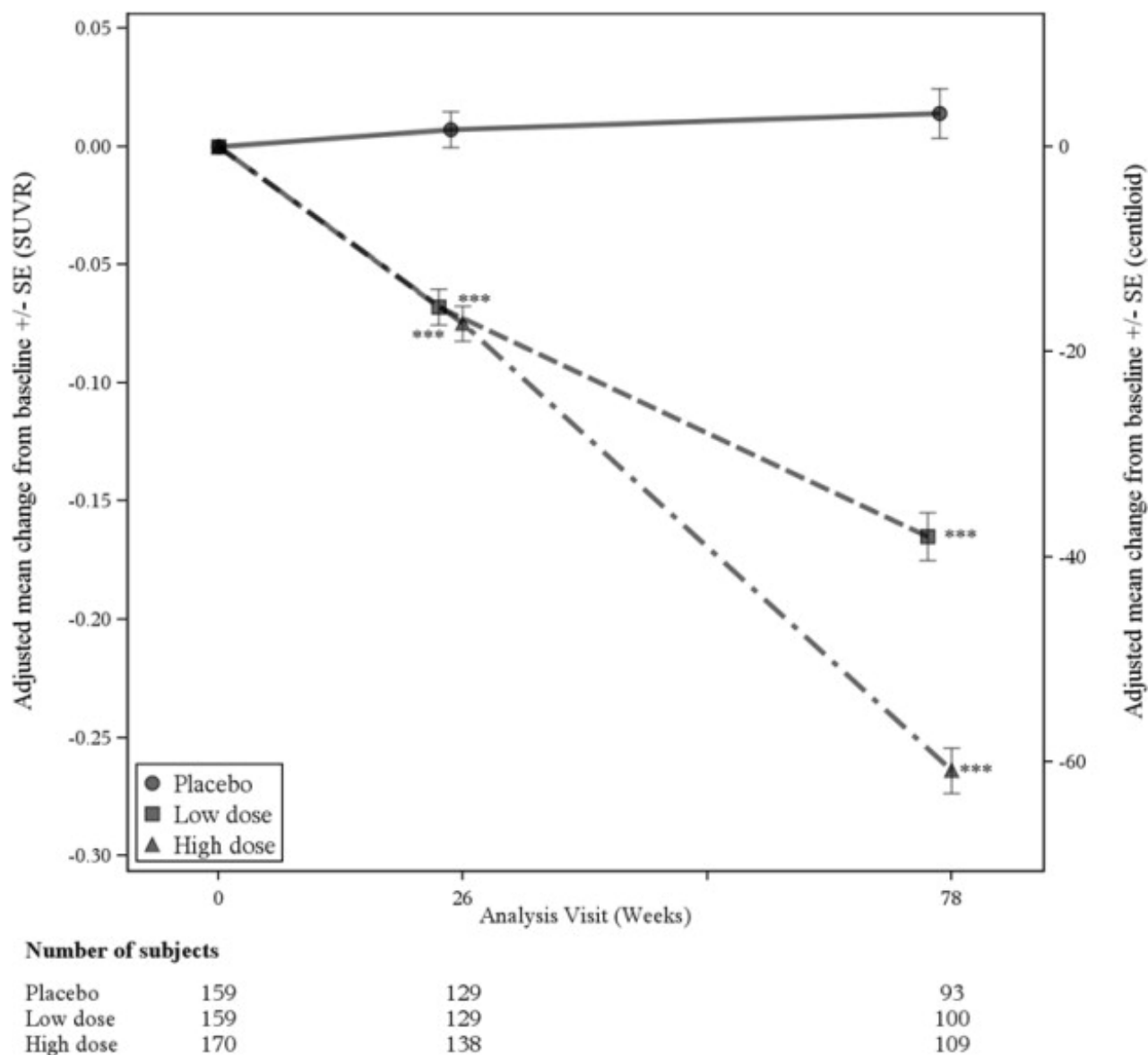
Studies 1 and 2 were terminated prior to their planned completion. Study endpoints were analyzed based on the prespecified statistical analysis plan.

Study 1

In Study 1, 1638 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years.

A subgroup of 488 patients were enrolled in the amyloid PET substudy; of these, 302 were evaluated at week 78. Results from the amyloid beta PET and CSF biomarker substudies are described in Figure 1 and Table 4.

Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1



*** p<0.001

Table 4: Biomarker Results of ADUHELM in Study 1

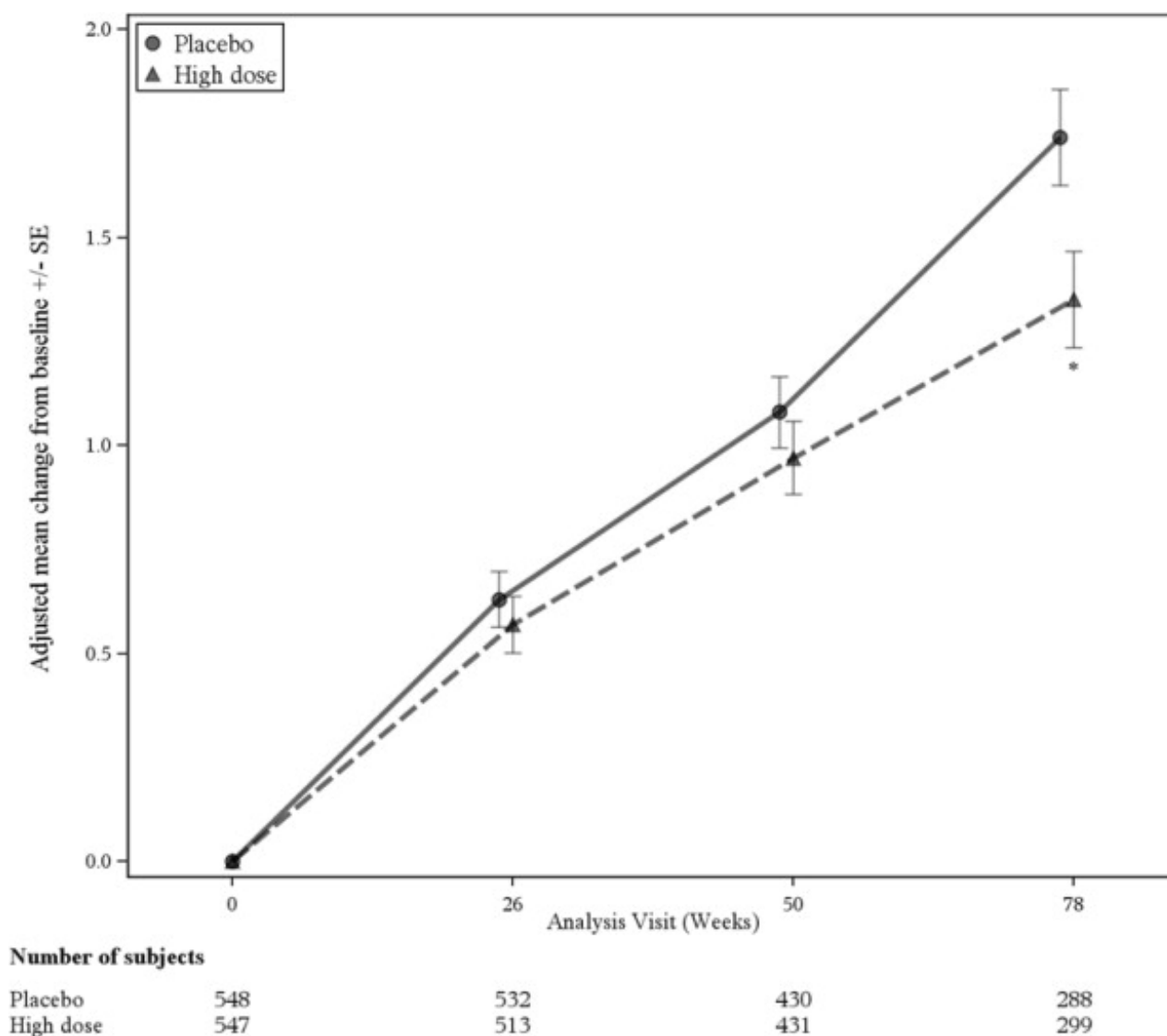
Biomarker Endpoint at Week 78 ¹	ADUHELM High dose	Placebo
Amyloid Beta PET Composite SUVR	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline	-0.264	0.014
Difference from placebo	-0.278, p<0.0001	
Amyloid Beta PET Centiloid	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline (%)	-60.8 (-71%)	3.4
Difference from placebo	-64.2, p<0.0001	
CSF p-Tau (pg/mL)	N=17	N=28
Mean baseline	100.11	72.55
Change from baseline	-22.93	-0.49

Difference from placebo	-22.44, p=0.0005	
CSF t-Tau (pg/mL)	N=17	N=28
Mean baseline	686.65	484.00
Change from baseline	-112.44	-0.39
Difference from placebo	-112.05, p=0.0088	

¹P-values were not statistically controlled for multiple comparisons.

The primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDR-SB) at Week 78. In Study 1, treatment with ADUHELM high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], p = 0.0120), as shown in Figure 2 and Table 5. The estimate of the treatment effect favored ADUHELM across all prespecified subgroups of interest.

Figure 2: Line Plot of Primary Efficacy Endpoint (Change From Baseline in CDR Sum of Boxes) in Study 1



* p<0.05

Secondary efficacy endpoints included the change from baseline in MMSE score at Week 78, the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78, and the change from baseline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score at Week 78. In Study 1, statistically significant differences from placebo were observed in the ADUHELM high dose group on all secondary efficacy endpoints evaluated. The estimate of the treatment effect favored ADUHELM across most prespecified subgroups of interest for the secondary efficacy endpoints. The Neuropsychiatric Inventory-10 item (NPI-10) was the only tertiary endpoint that assessed efficacy. The results of the high dose group, compared to placebo, are presented in Table 5.

Differences from placebo observed in the ADUHELM low dose group numerically favored ADUHELM but were not statistically significant.

Table 5: Clinical Results of ADUHELM in Study 1

Clinical Endpoint at Week 78	ADUHELM High dose (N=547)	Placebo (N=548)
CDR-SB		
Mean baseline	2.51	2.47
Change from baseline Difference from placebo (%)	1.35 -0.39 (-22%) p=0.0120	1.74
MMSE		
Mean baseline	26.3	26.4
Change from baseline Difference from placebo (%)	-2.7 0.6 (-18%) p=0.0493	-3.3
ADAS-Cog 13		
Mean baseline	22.246	21.867
Change from baseline Difference from placebo (%)	3.763 -1.400 (-27%) p=0.0097	5.162
ADCS-ADL-MCI		
Mean baseline	42.5	42.6
Change from baseline Difference from placebo (%)	-2.5 1.7 (-40%) p=0.0006	-4.3
NPI-10¹		
Mean baseline	4.5	4.3
Change from baseline Difference from placebo (%)	0.2 -1.3 (-87%) p=0.0215	1.5

¹P-value was not statistically controlled for multiple comparisons.

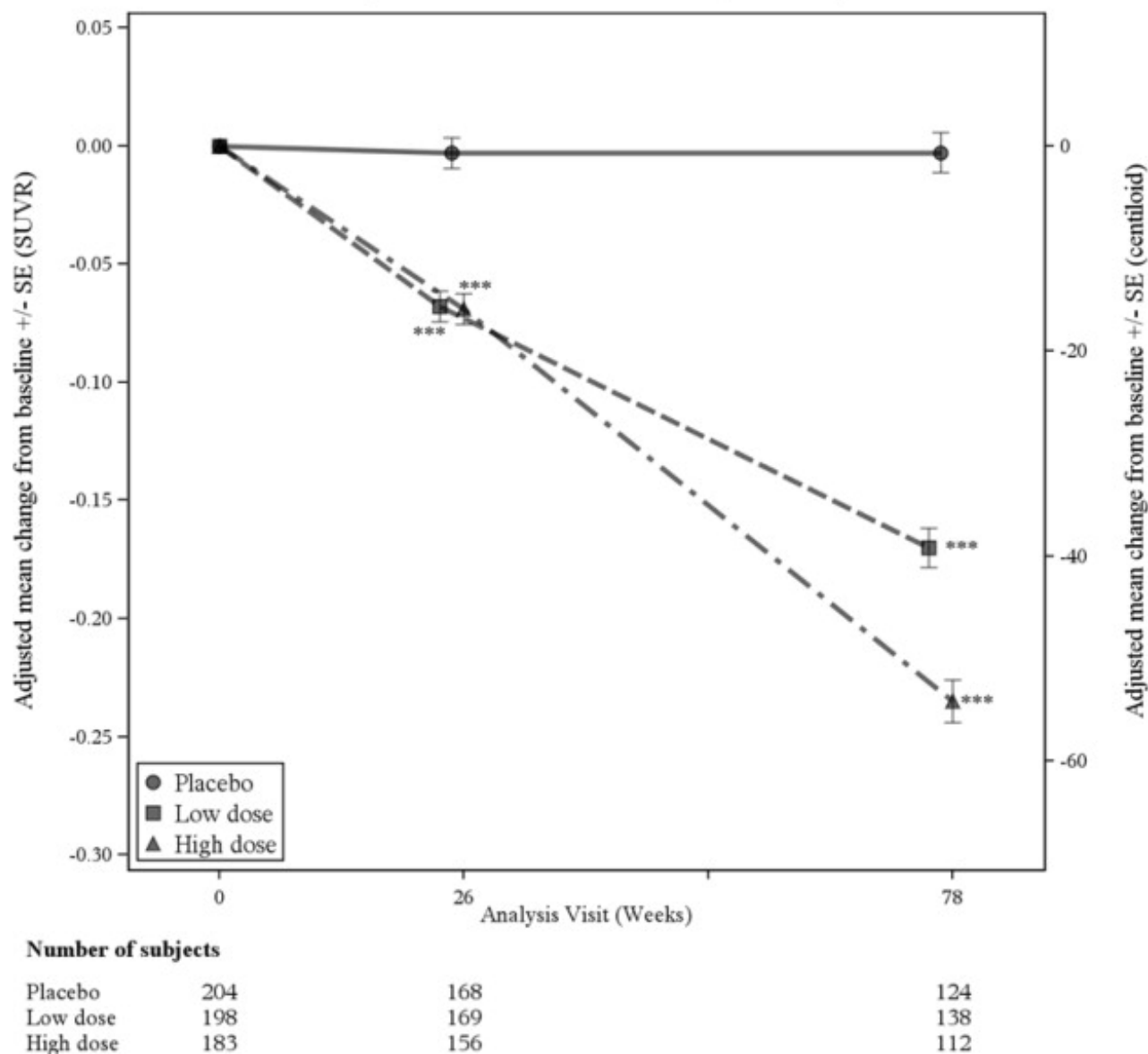
Study 2

In Study 2, 1647 patients were randomized 1:1:1 to receive ADUHELM low dose,

ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years.

A subgroup of 585 patients were enrolled in the amyloid PET subgroup; of these, 374 were evaluated at week 78. Results from the amyloid beta PET and CSF biomarker substudies are described in Figure 3 and Table 6.

Figure 3: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 2



*** p<0.001

Table 6: Biomarker Results of ADUHELM in Study 2

Biomarker Endpoint at Week 78 ¹	ADUHELM High dose	Placebo
Amyloid Beta PET Composite SUVR	N=183	N=204
Mean baseline	1.407	1.376

Change from baseline Difference from placebo	-0.235 -0.232, p<0.0001	-0.003
Amyloid Beta PET Centiloid	N=183	N=204
Mean baseline	90.8	83.8
Change from baseline (%) Difference from placebo	-54.0 (-59%) -53.5, p<0.0001	-0.5
CSF p-Tau (pg/mL)	N=18	N=15
Mean baseline	121.81	94.53
Change from baseline Difference from placebo	-13.19 -10.95, p=0.3019	-2.24
CSF t-Tau (pg/mL)	N=16	N=14
Mean baseline	618.50	592.57
Change from baseline Difference from placebo	-102.51 -69.25, p=0.3098	-33.26

¹P-values were not statistically controlled for multiple comparisons.

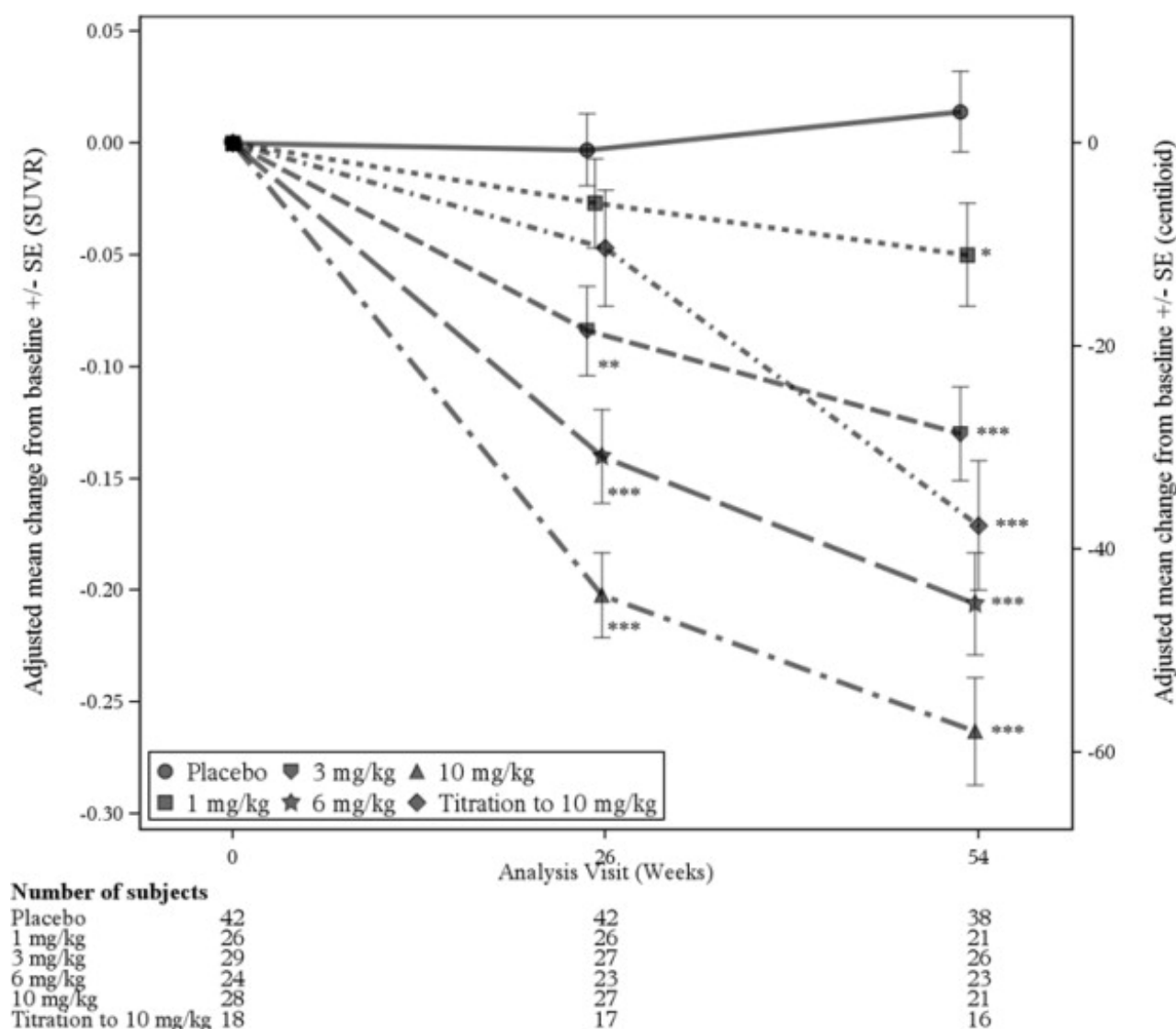
No statistically significant differences were observed between the ADUHELM-treated and placebo-treated patients on the primary efficacy endpoint, the change from baseline in CDR-SB score at 78 weeks.

Study 3

In Study 3, 197 patients were randomized to receive a fixed dose of ADUHELM 1 mg/kg (n=31), 3 mg/kg (n=32), 6 mg/kg (n=30), 10 mg/kg (n=32), titration of ADUHELM to 10 mg/kg over 44 weeks (n=23), or placebo (n=48) for 12 months. At baseline, the mean age of patients was 73 years, with a range of 51-91 years.

Results from the amyloid beta PET substudy are described in Figure 4 and Table 7.

Figure 4: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 3



* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 7: Biomarker Results of ADUHELM in Study 3

Biomarker Endpoint at Week 54¹	ADUHELM 10 mg/kg	Placebo
Amyloid Beta PET Composite SUVR	N=28	N=42
Mean baseline	1.432	1.441
Change from baseline	-0.263	0.014
Difference from placebo	-0.277, $p < 0.0001$	
Amyloid Beta PET Centiloid	N=28	N=42
Mean baseline	94.5	96.5
Change from baseline (%)	-58.0 (-61%)	3.1
Difference from placebo	-61.1, $p < 0.0001$	

¹P-values were not statistically controlled for multiple comparisons.

Clinical assessments in Study 3 were exploratory. Results for clinical assessments were directionally aligned with the findings from Study 1, with less change from baseline in CDR-SB and MMSE scores at 1 year in the ADUHELM 10 mg/kg fixed-dose group than in

patients on placebo (CDR-SB: -1.26, 95% CI [-2.356, -0.163]; MMSE: 1.9, 95% CI [0.06, 3.75]).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADUHELM (aducanumab-avwa) injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution. ADUHELM is supplied one vial per carton as follows:

170 mg/1.7 mL (100 mg/mL) single-dose vial (with red flip cap) – NDC 64406-101-01

300 mg/3 mL (100 mg/mL) single-dose vial (with blue flip cap) – NDC 64406-102-02

16.2 Storage and Handling

Unopened Vial

- Store in original carton until use to protect from light.
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Do not freeze or shake.
- If no refrigeration is available, ADUHELM may be stored unopened in its original carton to protect from light at room temperature up to 25°C (77°F) for up to 3 days.
- Prior to dilution, unopened vials of ADUHELM may be removed from and returned to the refrigerator if necessary, when kept in the original carton. Total combined time out of refrigeration with protection from light should not exceed 24 hours at room temperature up to 25°C (77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that ADUHELM may cause Amyloid Related Imaging Abnormalities or “ARIA”. ARIA most commonly presents as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, or nausea. Instruct patients to notify their healthcare provider if these symptoms occur. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA [see *Warnings and Precautions* (5.1)].

Hypersensitivity Reactions

Inform patients that ADUHELM may cause hypersensitivity reactions, including angioedema and urticaria, and to contact their healthcare provider if hypersensitivity reactions occur [see *Warnings and Precautions* (5.2)].

Manufactured by:
Biogen Inc.
Cambridge, MA 02142
US License #1697

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MEDICATION GUIDE

ADUHELM™ (AD-yew-helm)
(aducanumab-avwa)
injection, for intravenous use

What is the most important information I should know about ADUHELM?

ADUHELM can cause serious side effects, including:

Amyloid Related Imaging Abnormalities or “ARIA”. ARIA is a common side effect that does not usually cause any symptoms but can be serious. It is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain with the swelling. Although most people with swelling in areas of the brain do not have symptoms, some people may have symptoms, such as:

- headache
- dizziness
- nausea
- confusion
- vision changes

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with ADUHELM to check you for ARIA.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

What is ADUHELM?

- ADUHELM is a prescription medicine used to treat people with Alzheimer's disease.

It is not known if ADUHELM is safe and effective in children.

Before receiving ADUHELM, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if ADUHELM will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with ADUHELM.
- are breastfeeding or plan to breastfeed. It is not known if aducanumab-avwa (the active ingredient in ADUHELM) passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while receiving ADUHELM.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ADUHELM?

ADUHELM is given through a needle placed in your vein (intravenous (IV) infusion) in your arm.

ADUHELM is given every 4 weeks. Each infusion will last about 1 hour.

What are the possible side effects of ADUHELM?

ADUHELM can cause serious side effects, including:

- **See above “What is the most important information I should know about ADUHELM?”**
- **Serious allergic reactions.** Swelling of the face, lips, mouth, or tongue and hives have happened during an ADUHELM infusion. **Tell your healthcare provider if you have any of the symptoms of a serious allergic reaction during or after ADUHELM infusion.**

The most common side effects of ADUHELM include:

- swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain (ARIA)
- headache
- fall

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of ADUHELM.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. You can ask your pharmacist or healthcare provider for more information about ADUHELM that is written for health professionals. For more information, go to www.aduhelm.com or call at 1-833-425-9360.

What are the ingredients in ADUHELM?

Active ingredient: aducanumab-avwa

Inactive ingredients: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, and water for injection

Manufactured by: Biogen Inc., Cambridge, MA 02142, U.S. License #1697

ADUHELM is a trademark of Biogen. ©2021 Biogen and Eisai

This Medication Guide has been approved by the U.S. Food and Drug Administration

Approved: 6/2021

Principal Display Panel - 1.7 mL Carton Label

Rx Only

NDC 64406-**101**-01

Aduhelm™

(aducanumab-avwa)

Injection

170 mg/1.7 mL

(100 mg/mL)

For Intravenous Infusion Only

Must be diluted prior to use

ATTENTION: Dispense the enclosed Medication Guide to Each Patient.



Principal Display Panel - 3 mL Carton Label

Rx Only

NDC 64406-**102**-02

Aduhelm™

**(aducanumab-avwa)
Injection**

300 mg/3 mL
(100 mg/mL)

For Intravenous Infusion Only

Must be diluted prior to use

**ATTENTION: Dispense the enclosed
Medication Guide to Each patient.**



ADUHELM

aducanumab injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64406-101
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
aducanumab (UNII: 105J35OE21) (aducanumab - UNII:105J35OE21)	aducanumab	100 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
arginine hydrochloride (UNII: F7LTH1E20Y)	31.60 mg in 1 mL
histidine (UNII: 4QD397987E)	0.60 mg in 1 mL
histidine monohydrochloride monohydrate (UNII: X573657P6P)	3.39 mg in 1 mL
methionine (UNII: AE28F7PNPL)	1.49 mg in 1 mL
polysorbate 80 (UNII: 6OZP39ZG8H)	0.50 mg in 1 mL
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64406-101-01	1 in 1 CARTON	06/07/2021	
1		1.7 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761178	06/07/2021	

ADUHELM

aducanumab injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64406-102
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
aducanumab (UNII: 105J35OE21) (aducanumab - UNII:105J35OE21)	aducanumab	100 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
arginine hydrochloride (UNII: F7LTH1E20Y)	31.60 mg in 1 mL
histidine (UNII: 4QD397987E)	0.60 mg in 1 mL
histidine monohydrochloride monohydrate (UNII: X573657P6P)	3.39 mg in 1 mL
methionine (UNII: AE28F7PNPL)	1.49 mg in 1 mL
polysorbate 80 (UNII: 6OZP39ZG8H)	0.50 mg in 1 mL
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64406-102-02	1 in 1 CARTON	06/07/2021	
1		3 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761178	06/07/2021	

Labeler - Biogen Inc. (121376230)

Revised: 6/2021

Biogen Inc.